CBER Perspectives on the Opportunities and Challenges of Using Disposables in Biopharmaceutical Production

Biopharm Manufacturing and Distribution Summit

Disposables for Biopharm Production: Integrating New technology for Safety, Cost Savings and Speed to Market

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Presentation Outline

- Emphasis on what CBER has found as being opportunities and challenges in the use of disposables in the areas of:
  - Providing alternatives to fixed asset production technologies
  - Providing improvements to existing manufacturing schemes
  - Providing for manufacturing of patient customized therapies
  - Equipment suitability assessment and validation
  - Lessons learned from inspectional findings
  - Avoiding problems down the road: Assessing risks during process development and design

Some Uses of Elastomers

- Liquid process path contact (bags, containers, and connectors)
  - Bags/Containers – used as bioreactors, storage and/or processing containers, in-process hold containers, and side sample pouches, etc.
  - Tubing/specialized assemblies – fluid transfers and connectors
  - Closures and primary packaging (clinical presentation containers) – stoppers, blow/fill/seal, form/fill/reseal, etc.

Disposable Bags - Opportunities

- Scalability advantages claimed in some situations
- Decreases validation demands in areas of cleaning and containment in some situations
- Decreased initial capital costs for fixed manufacturing equipment assets

Disposable Bags - Challenges

- Biocompatibility and extractable issues
- Dependence of manufacturer on an outside vendor for critical processing equipment – potential impact of changes in polymer production or product availability could have significant impact on production scheduling
- Due diligence in defining fitness-for-use criteria and inventory control to provide for continuous market supply
- Demonstration of product quality characteristics if operation parameters impacted by limitations under some circumstances

Disposable Bags –Bioreactors

- Characterization of cell culture operations using bags should include assessment of measures of growth, control, productivity, and product quality
- Potential differences compared to fixed tanks; hollow-fiber/perfusion; fluidized bed; T-flasks and roller bottles: differing shear force and oxygen transfer rate issues

Disposable Bags –Bioreactors

- Measurement and control capability for Temp, CO_2, O_2, and pH may differ
- Strength of the product characterization capability (peptide and glycan maps, HPLC, etc.) may impact expectations of regulatory agencies relative to demonstrating product comparability – early discussion with regulatory officials recommended

Disposable Bags –For Storage

- Freeze thaw dynamics
- Integrity testing of integrated filters
- Provisions for sampling
- Glass transition temperature of polymers relative to intended use temperatures

Growth Condition Effects

- During development phase, it is important to have a full understanding of cell behavior under varying growth conditions and to consider impacts as equipment systems are chosen…
- Possible concerns:
  - Cell responses to differing means of propagation (tank, perfusion, roller bottle, cell factories, etc.)
  - Potential impact of pressure changes on viability of attachment dependent cells
  - Microenvironment effects - localized differences in dissolved gases, nutrient availability, physicochemical measures (e.g., pH, osmolality, etc.)

Process Design

- Choice of growth conditions utilized combined with robustness of cell growth characteristics can greatly impact process output
- Choice of equipment supporting cell culture can impact on degree of control required
  - e.g., roller bottles require a number of aseptic manipulations that increase the possibility of contamination compared to tanks with steam-in-place addition/sampling ports

Process Design Factors - 1

- Examples:
  - Scale-up tank bioreactors -> changes in water column height; changes in pressure and potential impacts on cell attachment to carriers
  - New tank bioreactor -> changes in mixing dynamics, potential multiple toroid/toroid-like mixing patterns leading to poor nutrient or gas exchange uniformity
  - Changes in cell culture stress -> potential induction of endogenous retroviral particles, especially in certain murine cell lines

Process Design Factors - 2

- Examples (continued):
  - Adequate rate of perfusion for nutrients/gases and removal of wastes for hollow fiber systems?
  - Cell growth characteristics under perfusion conditions?
  - Variability of expression of recombinant protein constructs due to nutrient dynamics under perfusion versus tank growth conditions?
  - Differences in oxygen transfer rate and impact on cell growth?

Equipment: Suitability Assessment and Validation - 1

- Capable of function under all intended physical conditions? (i.e., operating ranges for temperature, pressure, pH, etc)
- Capable of supplying the culture with needed nutrients, dO/dCO2 and environmental control?
- Capable of maintaining culture purity? (sterilizable input/sampling ports, sterile fluid addition capability, sanitary valves, tube welding methods used, etc.)

Equipment: Suitability Assessment and Validation - 2

- Use of elastomeric contact materials
  - Glass transition temperature of the plastic and potential for brittleness with low temperature processing?
  - Tube welding process reproducible and robust?
  - Biocompatibility of elastomers, processing aids, lubricants, etc?
  - Adsorptive properties and impact on growth promoting characteristics of media (e.g., availability of cholesterol in serum free media)

Changing existing processes ?

- Alternatives are being made available that can allow the number of open manipulations to be minimized. For example:
  - May allow aseptic connections to be formed under a greater degree of control than manual connections made under Class A conditions
  - May afford greater containment of process stream, where desirable
  - May assist in minimizing operator to operator variability of processing steps

Opportunities in clinical development..

- Extensive use in *ex vivo* manipulations of tissues and cells in the growing field of cellular therapies
  - Single-use, sterile, disposable bag systems often with complex side assemblies for sampling or processing step transfers
  - Cell sorter chambers for *ex vivo* cell class enrichment protocols

Lessons Learned: Inspection (PAI) Findings

- The most common cell culture issues noted during PAIs are related to:
  - characterization of the cells and construct stability,
  - characterization of the product and any potential variability, and
  - maintaining purity of culture for cells or seeds.

Lessons Learned: Inspection (PAI) Findings

- The most common elastomer issues noted during pre-approval inspections (PAIs) are related to:
  - equipment-related failures in processing,
  - documentation of extractable profile characterization
  - vendor qualification and/or fitness-for-use criteria definitions

Lessons Learned: Inspection findings

- The most common issues noted during inspections (PAI and biennial) are related to:
  - failure to follow procedures (leading to process failure),
  - failures in quality unit responsibilities or functions, and
  - other pure GMP failures in manufacturing control

Lessons Learned: Inspection findings

- Many concerns not directly linked to manufacturing can be traced back to issues related to:
  - vague descriptions of procedures in documentation,
  - poor communications between various disciplines (e.g., process science, process engineering, facility engineering, quality operations, validation unit, etc.) while defining validation or fitness-for-use criteria, and/or
  - failure to take action when needed (sometimes due to unclear definition/understanding of responsibilities or authority to perform specific tasks)

How can we avoid some of these pitfalls?

Most likely causes of problems…

- Communication often root cause of delays in getting a process approved and the product to market
- Critical to have all disciplines involved in defining and developing process steps and operational parameters
- Having sufficient resources and time allotted for bringing process to commercial scale
- Acting on internal quality unit recommendations

How can we avoid some of these pitfalls?

- Enhance internal communications across organizational units and disciplines, if not optimal
- Designing the process so that robust equipment systems and production platforms can be supported
- Planning for the procedural controls that will need to be implemented to maintain consistent process performance
- Identifying the weaknesses early in the design process so that mitigation can be built into the process

Assessing the Process: *"Risk Based Quality"*

- Risk Management = dynamic and interactive use of Risk Assessment and Risk Mitigation
- Prospective *versus* Reactive Risk Assessment
  - Initial Process Mapping to outline initial validation plan and/or process control strategy
  - Problem identification process may be used by industry or regulators (e.g., deviation system or quality system inspections)
- *Relationship to Critical Process Parameters ?*

Relationship between validation and risk: What is Validation?

- "Proof of validation is obtained through rational experimental design and evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase." (Compliance Policy Guide 7132c.08)
- How does one achieve "rational experimental design" ?
  - COMMUNICATION between organizational units and multi-disciplinary ANALYSIS of the specific operation

Is there really something new here?

- Yes and No
- ***Informal*** risk assessments have been performed for many years
- A more formalized risk assessment ***may*** assist in identifying possible hazards prior to initiation of developmental studies and/or validation/qualification studies AND provide a formal mechanism to encourage multi-disciplinary discussion and communication

Summary of Risk Assessment Approaches

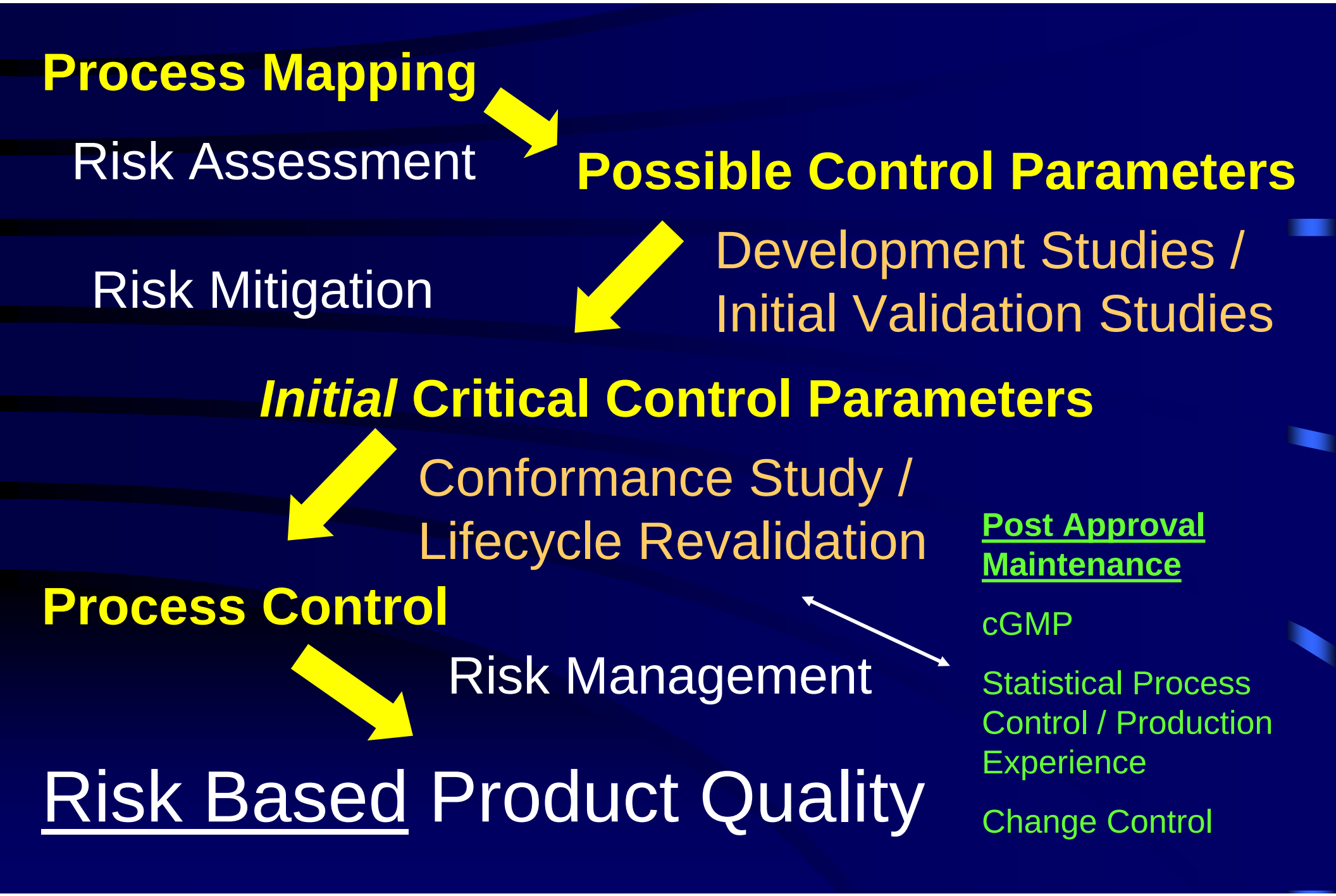
- Process Mapping is pre-requisite of risk assessment
- Various formalized approaches exist (e.g., PHA, HACCP, HAZOP, FTA, FMEA, FMECA, etc.) – Risk Management tools
- Risk Ranking and Filtering – compare and prioritize risks
- Supporting Statistical Tools (DOE, Process Capability Analysis, Control Charts, etc.)
- Informal Risk Management – *Why use more formalized approach?*

Some early priorities include:

- Prioritization of safety related qualification and validation activities
- Performing equipment capability assessments for each unit operation as processing parameters are defined
- Often new risk factors may be identified when equipment is undergoing initial usage, especially for emerging technologies where equipment performance and fitness-for-use criteria may not be well understood

Immediate Risk Related Concerns: Hazard Analysis and Evaluation

- Safety related issues:
  - Adventitious agents,
  - Maintaining sterility, culture purity, or bioburden control,
  - Immunogenicity concerns, etc.
- Process consistency:
  - Process alteration and optimization
  - Process scale up impacts
    - May be confounded by ongoing qualification and validation activities


Process Mapping
Risk Assessment
Possible Control Parameters
Development Studies /
Initial Validation Studies
Risk Mitigation
Initial Critical Control Parameters
Conformance Study /
Lifecycle Revalidation
Post Approval Maintenance
cGMP
Statistical Process Control / Production Experience
Change Control
Process Control
Risk Management
Risk Based Product Quality

Risk Mitigation: Purpose of Testing

To verify that all processes and systems continue to function (as designed) on a routine basis …

AND

…that product meets quality expectations reflecting clinical experience.

Risk Mitigation: Testing Program

The process is dynamic and varies from product to product. For example:

- Suitability of raw materials
- Operating status of equipment/facility/personnel supporting a unit operation
- Suitability of material generated by a unit operation for continued production – you may want to include an approach including assessment of “end user requirements” in defining criteria for specific steps
- Suitability of final product for use


A QUALITY PRODUCT
QA/QC
Validation / Qualification
Routine Monitoring
Risk Assessment/Mitigation
Equipment
Environment
Process
Raw Materials
Components

Summary - 1

- Manufacturing operations are complex and very dynamic, thus controlling the performance of the process requires understanding of the multiple variables and how they impact each other.
- Careful consideration during the process design stage can be very beneficial and contribute to successful implementation of a well-controlled and reliable production system.
- Variables impacted by multiple disciplines; therefore, multiple organizational units. Fostering open communication throughout process development will enhance ability to capture all critical aspects for validation and qualification activities earlier in the process (decrease needs for revalidation or managing non-conformance later in the process development cycle)

Summary - 2

- A structured risk management approach may assist in defining the important aspects to assess during early process development and subsequent validation activities
- Fitness-for-use criteria for equipment should be identified early in the process and based in early developmental studies to forego later complications, if feasible
- FDA is open to discussions of specific aspects of process design throughout the product development cycle. Early communication with FDA is encouraged
- REMINDER: Once the process is designed and validated, robust quality unit required to oversee operations to ensure continued success. One of the major causes for compliance concerns after approval of a commercial process is shortcomings of a quality operations unit